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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/751,451	KAWAI ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/701,121.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/6/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 are pending.

2. Applicant's election with traverse of Group 1, Claims 1-4 and 6-10 drawn to a monomer protein comprising an amino acid sequence belonging to TGF-β superfamily, of which cysteine related to a dimmer formation of the protein has been replaced with another amino acid, and an agent comprising said monomer, filed 1/12/06, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

   The request for rejoinder of the non-elected method (claim 5) upon an indication of allowance of the product claim is acknowledged. However, no product is allowable at this time.

3. Claim 5 is withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

4. Claims 1-4 and 6-10, drawn to a monomer protein comprising an amino acid sequence belonging to TGF-β superfamily, of which cysteine related to a dimmer formation of the protein has been replaced with another amino acid, and an agent comprising said monomer, are being acted upon in this Office Action.

5. Applicant should amend the first line of the specification to update the relationship between the instant application and 09/701,121, filed 1/3/01, which is now abandoned.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4 and 6-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a monomeric protein comprising the amino acid sequence described in SEQ ID NO: 2 of the Sequence Listing for inducing the differentiation of osteoblast by measuring alkaline phosphatase activity, **does not** reasonably provide enablement for (1) *any*

monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid, (2) *any* monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid, or any other amino acid selected from the group consisting serine, threonine, alanine and valine, (3) *any* monomer protein comprising "an" amino acid sequence described in SEQ ID NO: 2 of the Sequence Listing, and (4) *any* agent comprising *any* monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid, containing an effective amount of said monomer protein for "preventing" *any* disease affecting bone and/or cartilage, any disease affecting bone and/or cartilage such as osteoporosis, osteoarthritis or arthrosteitis, any bone fracture, any disease that lacks root of teeth and tooth socket. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The scope of the term monomer protein and agent includes numerous members (genus) and variants of TGF-β superfamily having a cysteine related dimmer formation be replaced with another amino acid for "preventing" and treating all diseases affecting bone and/or cartilage.

The specification discloses only one monomer protein comprising *the* amino acid sequence of SEQ ID NO: 2 that belongs to the TGFβ superfamily, wherein the cysteine at position 83 of SEQ ID NO: 2 has been substituted for alanine and wherein the monomer protein induces differentiation of osteoblast by measuring alkaline phosphatase activity (See page 5, lines 10-15, pages 12-13).

Other than the specific monomer protein mentioned above, the specification does not teach how to make and use *any* monomer protein and *any* agent mentioned above for "preventing" and treating *any and all* diseases affecting bone and/or cartilage without the amino acid sequence.

The specification does not teach which amino acids within the full-length sequence of all monomeric protein are critical and can or cannot be change such as substitution, deletion, addition and combination thereof. The specification does not teach any assays that is useful for screening variants and is predictive of success in vivo.

It is known in the art that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein.

Ngo *et al* (PTO 892) teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Mason *et al* (PTO 1449) teach in activin A, a member of the TGFβ superfamily, even a single amino acid substitution from cysteine to alanine fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular), resulting in losses biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) and losses of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach an equivalent protein such as TGFβ1 in which replacing cysteine residue for a serine residue resulted in loss bioactivity (See page 330, column 1, first paragraph, in particular).

Given the unlimited number of monomer protein and agent, there is a lack of in vivo working example showing that any undisclosed monomeric protein, particularly the fragment thereof (claim 4) and agent are effective for treating any disease affecting bone and/or cartilage let alone for "preventing" any and all diseases affecting bone and/or cartilage such as osteoporosis, osteoarthritis or arthrosteitis, any bone fracture, any disease that lacks root of teeth and tooth socket. The actual biological activity and that of the monomer protein, agent and fragment of SEQ ID NO: 2 per se in the bone and/or cartilage remain to be demonstrated. As such, treatment of disease affecting bone and/or cartilage mentioned above using any monomer protein and agent comprising any monomer proteins is highly unpredictable, varies depending on the animal model, means of administration and composition of the monomer protein. Let alone

the undisclosed monomer protein and agent comprising the undisclosed protein is use for "preventing" any and all diseases affecting bone and/or cartilage mentioned above.

Since the structure of the monomer protein is not enabled, any agents comprising any undisclosed monomer protein for preventing and treating any disease affecting bone and/or cartilage mentioned above are not enabled.

With regard to monomer protein comprising "an" amino acid sequence described in SEQ ID NO: 2, the term "comprising an amino acid sequence" encompasses amino acid sequence that comprise the full-length sequence of SEQ ID NO: 2 or any portion of SEQ ID NO: 2. There is not a single fragment from the smallest to the largest fragment of SEQ ID NO: 2 show any biological effect in vitro or in vivo, much less for "preventing" and/or treating any and all diseases affecting bone and/or cartilage mentioned above.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 1-4 and 6-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid, (2) *any* monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid wherein another amino acid is an amino acid selected from the group consisting serine, threonine, alanine and valine, (3) any monomer protein comprising "an" amino acid sequence described in SEQ ID NO: 2 of the Sequence Listing, and (4) *any* agent comprising *any* monomer protein

comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid, containing an effective amount of said monomer protein for "preventing" *any* disease affecting bone and/or cartilage, any disease affecting bone and/or cartilage such as osteoporosis, osteoarthritis or arthrosteitis, any bone fracture, any disease that lacks root of teeth and tooth socket.

The scope of the term monomer protein and agent includes numerous members (genus) and variants of TGF-β superfamily having a cysteine related dimmer formation be replaced with another amino acid for "preventing" and treating any disease affecting bone and/or cartilage.

The specification discloses only one monomer protein comprising the amino acid sequence of SEQ ID NO: 2 that belongs to the TGFβ superfamily, wherein the cysteine at position 83 of SEQ ID NO: 2 has been substituted for alanine and wherein the monomer protein induces differentiation of osteoblast by measuring alkaline phosphatase activity (See page 5, lines 10-15, pages 12-13).

Other than the specific monomer protein comprising the amino acid sequence of SEQ ID NO: 2 mentioned above for induces differentiation of osteoblast, there is inadequate written description about the structure associated with function of *any* monomer protein, *any* agent comprising any monomer protein, and any portion of an amino acid sequence of SEQ ID NO: 2 mentioned above without the amino acid sequence.

The specification does not adequately describe the structure of the genus of monomer protein from the TGF-β superfamily, much less the function of the monomer protein having cysteine related to dimmer formation replaced. The specification does not describe which amino acids within the full length sequence of any and all monomer proteins can or cannot be change and what biological activity the modified monomer protein has in vitro or in vivo. Let alone the modified monomer protein or agent comprising the modified monomer protein is use for "preventing" and/or treat any and all diseases affecting bone and/or cartilage, any diseases affecting bone and/or cartilage such as osteoporosis, osteoarthritis, arthrosteitis, bone fracture, or any disease that lacks root of teeth or tooth socket. Since the structure of the monomer protein is not adequately described, any agents comprising any undisclosed monomer protein are not adequately described.

Regarding monomer protein comprising "an" amino acid sequence described in SEQ ID NO: 2, the term "comprising an" encompasses amino acid sequence that comprise the full-length sequence of SEQ ID NO: 2 or any portion of SEQ ID NO: 2. There is not a single fragment from

the smallest to the largest fragment of SEQ ID NO: 2 have been described in the specification as filed. There is not a single fragment from the smallest to the largest fragment of SEQ ID NO: 2 show any biological effect and useful for preventing and/or treating any disease affecting bone and/or cartilage.

The specification discloses only one monomer protein comprising the amino acid sequence of SEQ ID NO: 2 having only one amino acid substitution from cysteine to alanine which corresponds to position 83 of SEQ ID NO: 2, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of monomer protein and agent comprising monomer protein to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-3 and 6-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Mason *et al* (Molecular Endocrinology 8(3): 325-332, 1994; PTO 1449).

Mason *et al* teach a monomer protein or agent such as activin A comprising an amino acid sequence that belongs to the TGF-β superfamily of which cysteine at position 80 related to a dimmer formation of the protein has been replaced with another amino acid such as alanine or serine (see page 327, column 1, in particular). Claims 6-10 are included in this rejection because the agent comprising the same monomer protein. A product is a product, irrespective of it's intended use. Thus, the reference teachings anticipate the claimed invention.

11. Claims 1-3 and 6-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Brunner et al (J Biol Chem 264(23): 13660-13664, 1989; PTO 892).

Brunner et al teach a monomer protein or agent such as transforming growth factor β1 precursor that belongs to the TGF-β superfamily of which cysteine at position 223 and 225 that related to a dimmer formation of the protein has been replaced with another amino acid such as serine (see abstract, page 13661, column 1, Figure 2, in particular). Claims 6-10 are included in this rejection because the agent comprising the same monomer protein. A product is a product, irrespective of it's intended use. Thus, the reference teachings anticipate the claimed invention.

12. Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated US Pat No 5,658,882 (Aug 19, 1997; PTO 892)

The '882 patent teaches a monomeric polypeptide comprising an amino acid sequence such as Phe Pro Leu Arg Ser His Leu Glu Pro Thr Asn of SEQ ID NO: 6 (see reference SEQ ID NO: 6 residues 15 to 25, which corresponds to residues 53 to 63 of claimed SEQ ID NO: 2, in particular). The term "comprising *an* amino acid sequence" encompasses amino acid sequence that comprises the full-length sequence of SEQ ID NO: 2 or any portion of claimed SEQ ID NO: 2. The '882 patent teaches a portion of claimed SEQ ID NO: 2. Further, the term "comprising" is open-ended. It expands the portion to include additional amino acids at either or both ends to include the reference peptide. The reference peptide inherently is monomeric because the short peptide does not contain the two cysteine residues related to dimmer formation of SEQ ID NO: 2 (cysteine residues 83-84 of claimed SEQ ID NO: 2). Thus, the reference teachings anticipate the claimed invention.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

15. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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